

PATENT
144002-2001**REMARKS**

Reconsideration and withdrawal of the objections to and rejections of this application are respectfully requested in view of the amendments and remarks herewith.

STATUS AND FORMAL MATTERS

Claims 1 to 26 are pending in this application. Claim 12 is canceled without prejudice or any intent to create any estoppel as to equivalents. Claims 13 to 26 are added without prejudice or any intent to create any estoppel as to equivalents. Applicant reserves the rights to pursue canceled subject matter in a continuation application.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims are in full compliance with the requirements of 35 U.S.C. §112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments are made simply for clarification and to round out the scope of protection to which Applicant is entitled. Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel, as the herewith amendments are not narrowing amendments.

The Examiner is thanked for withdrawing her various objections and rejections to claims 1 and 3-5 as set forth on page 3 of the previous Office Action (March 4, 2003). Applicant thanks the Examiner for the courtesy granted to his legal representative in granting a telephonic interview on February 5, 2004.

Applicant disagrees with the rejections presented in the October 7, 2003 Office Action, however, in the spirit of expediting prosecution of this patent application, claim 12 is

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canceled, without prejudice, without admission, without surrender of subject matter and without any intention to create any estoppel as to equivalents.

No new matter is added.

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the amendments and remarks herein, which places the application in condition for allowance.

THE REJECTIONS UNDER 35 U.S.C. § 102(a) ARE OVERCOME

The Examiner maintains her rejection of claim 1 under 35 USC §102(a) as allegedly being anticipated by Bruchfeld et al. (Journal of the American Society of Nephrology, September, 2000, Vol. 11, No. Program and Abstract Issue, pp. 57A.) ("Bruchfeld"). (*see* October 7, 2003 Office Action, at 2 to 3). The rejection is traversed.

The present invention teaches and discloses a new use for erythropoietin ("EPO"), such as EPO alpha, in treating ribavirin ("RBV") and interferon-alpha ("IFN") induced anemia. More specifically, the present invention can be administered to humans as well as animals infected with Hepatitis C virus ("HCV") or Human immunodeficiency virus ("HIV") or HIV and HCV or who are suffering from anemia, in particular, RBV or RBV and IFN induced anemia. Accordingly, the present invention teaches using EPO with HCV treatment, such as RBV and/or IFN. Thus, the invention pertains to a method of administering and/or co-administering EPO, RBV and IFN, or EPO and RBV, compositions thereof and kits containing EPO, RBV and IFN or EPO and RBV. Specifically, the present invention teaches a method of administering EPO to patients with RBV-induced anemia in order to enable HCV-infected patients to receive the maximum effective dosage of RBV and IFN necessary to eradicate HCV. The invention also teaches using EPO with RBV and/or IFN treatment in patients who do not have chronic renal

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disease such that the RBV dosage can be administered at the maximum effective amount necessary to eradicate HCV. EPO can be administered in a liquid preparation and/or administered as a vector for *in vivo* expression. Moreover, the present invention also evaluates the clinical benefit of EPO in RBV and IFN-induced anemia.

As currently presented, claim 1 of the present invention is directed to a method for treating an HCV infection in an HIV-negative patient by administering RBV or RBV and IFN alone with the administering of EPO wherein the RBV can be administered at a maximum effective dosage necessary to eradicate HCV.

The Office Action contends that Bruchfeld anticipates claim 1 under 35 U.S.C. § 102(a) since it teaches the treatment of HCV infection with IFN and RBV and further, that the RBV-induced anemia can be managed with EPO. Applicant respectfully disagrees.

It is respectfully submitted that Bruchfeld relates to, *inter alia*, (1) lower daily dosages of RBV which are not effective to eradicate HCV, (2) managing anemia by using EPO and low-dose iron, and (3) treating patients who suffer from chronic renal disease.

Because the present invention teaches treating patients who do not have chronic renal disease, ribavirin (RBV) can be administered at a maximum effective dosage necessary to eradicate hepatitis C. In addition, because the patient group in the present invention does not have chronic renal disease, it is not necessary to use iron to control or manage the ribavirin-induced anemia.

Accordingly, the present invention is neither taught nor disclosed in Bruchfeld. In fact, Bruchfeld teaches away from the present invention. Accordingly, Bruchfeld does not anticipate claim 1 of the present invention.

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"[F]or a prior art reference to anticipate in terms of 35 U.S.C. 102(a), every element of the claimed invention must be identically shown in a single reference." *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991). Bruchfeld does not teach administering ribavirin at a maximum effective dosage (Bruchfeld teaches administering 170 to 300 mg/daily of RBV) to patients since the patients in Bruchfeld all suffer from chronic renal disease. More particularly, Bruchfeld stated that treatment "requires reduced ribavirin doses as well as close monitoring of ribavirin concentration." (See lines 34-35 of Bruchfeld). And, as admitted by Bruchfeld, HCV was indeed not eradicated by the administration of the RBV dosages used by Bruchfeld. In particular, Bruchfeld stated that "4/5¹ dialysis patients became HCV-RNA negative during treatment, but relapsed post-treatment." (See lines 29-32 of Bruchfeld). That the HCV-RNA reappeared in the treated patients necessarily means that the HCV was not eradicated, which is in stark contrast to the present invention as claimed and disclosed. Thus, Bruchfeld does not anticipate claim 1 as alleged in the Office Action.

Moreover, that Bruchfeld requires reduced doses of RBV. This represents a teaching away from the instant invention since the notion of requiring lower doses of RBV is in line with a strategy to administer lower dosage of RBV in order to counter-balance RBV-induced anemia. In particular, the present invention points to Jen et al., *Population Pharmacokinetic and Pharmacodynamic Analysis of Ribavirin in Patients with Chronic Hepatitis C*, Therapeutic Drug Monitoring, Vol.22 No.3, 2000, where it stated that "anemia is a well-established adverse effect of ribavirin therapy [and] [f]rom a practical perspective, the most appropriate method of dealing with treatment related anemia would appear to be through dose reduction of ribavirin." (see page 5, lines 8-21 of the present application; emphasis added).

¹ A fifth patient died during treatment due to heart failure (see line 22 of Bruchfeld).

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Bruchfeld, consistent with Jen et al's teaching, discloses administering a low level of RBV that is seven times less than the RBV levels taught in the present invention. The lower RBV dosage used by Bruchfeld could have the undesirable consequence of reducing the effectiveness of the antiviral treatment for the eradication of the HCV from the infected patient. Indeed, based on Bruchfeld's own assertion, all patients treated relapsed as to the HCV infection. (See line 30 of Bruchfeld). Thus, Bruchfeld does not teach eradicating HCV by administering RBV at a maximum effective dosage as claimed and disclosed in the present invention.

In addition, Applicant respectfully asserts that the Bruchfeld does not disclose a method for treating RBV-induced anemia with the administering of EPO alone, but rather a method that requires the administration of both low-dose iron and EPO together. In particular, Bruchfeld states that "[r]ibavirin induced anemia was managed with low-dose iron as well as erythropoietin." (See line 29 of Bruchfeld). Thus, although Bruchfeld states in its conclusion that RBV-induced anemia can be "managed" with EPO, the method of Bruchfeld, in fact, included the administration of low-dose iron. This is in stark contrast to the present invention, which does not disclose or claim the administration of iron.

More in particular, claim 1 is not drawn to the use of low-dose iron to treat RBV-induced anemia. Instead claim 1 is drawn to a method for treating an HVC patient by administering RBV or RBV and IFN and the administering of EPO concomitantly, sequentially, or via co-administration with RBV or RBV and IFN. Neither the claim nor the disclosure teaches administering or co-administering iron, in particular, to treat RBV or RBV and IFN induced anemia.

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Accordingly, Bruchfeld does not anticipate claim 1. Reconsideration and withdrawal of the rejections to claim 1 under 35 U.S.C. § 102(a) based on Bruchfeld is respectfully requested.

THE REJECTIONS UNDER 35 U.S.C. § 103(a) ARE OVERCOME

Claims 2-5 and 7-11 are rejected under 35 U.S.C. § 103(a) as said to be unpatentable over Bruchfeld in view of Niitsu et al., U.S. Patent No. 6,268,336 ("Niitsu"). (October 7, 2003 Office Action, at pages 3 to 4). The rejections are traversed and will be addressed collectively.

Claim 12 is now canceled and thus the rejection of claim 12 under 35 U.S.C. § 103(a) is moot.

The alleged teachings of Bruchfeld are outlined above. Niitsu allegedly relates to a pharmaceutical composition for treatment of hepatic diseases, in particular for treatment of venesection-induced anemia in HCV patients. However, Niitsu, as pointed out by the Examiner, "does not teach the administration of RBV, IFN and EPO in patients co-infected with HCV and HIV." (March 4, 2003 Office Action, at page 7).

Claims 2-5 and 8 have been amended consistent with the amendment to claim 1 discussed above, namely that the RBV administered i at a maximum effective dosage necessary to eradicate HCV. In accordance with the reasoning outlined above, Bruchfeld fails to qualify as prior art under 35 U.S.C. § 102 since it does not teach or disclose using the maximum effective dosage of RBV, does not teach the eradication of HCV, and does not teach a regime of EPO but rather a required combination regime of low-dose iron and EPO for the alleviation of RBV-induced anemia. Accordingly, Bruchfeld cannot be used as a basis for a rejection to claims 2-5 and 7-11 under 35 U.S.C. § 103(a) since Bruchfeld does not teach or disclose each and every

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element of the claims. In fact, Bruchfeld teaches away from the present invention. Further, Niitsu does not teach or disclose combining IFN and RBV to treat HCV patients, nor does it teach the co-administration of IFN/RBV and EPO. Therefore, Applicant respectfully submits that Bruchfeld and Niitsu either alone or in combination does not teach the invention as claimed and disclosed..

Even if Bruchfeld alone or in combination with Niitsu taught or disclosed each and every element of the present invention, which is not the case, there is no teaching nor motivation to suggest the combination of these two references and thus, the 103(a) rejections cannot stand.

In an obviousness rejection, the standard established in *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783-84 (Fed. Cir. 1992), must be followed. *Fritch* in pertinent part states (with emphasis added):

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under Section 103, teachings of references can be combined only if there is some suggestion or incentive to do so **The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification.**

Even if a reference can be modified in a way that the Examiner suggests, this does not mean that the reference renders the instant invention obvious unless the motivation to make the modification suggested by the Examiner is in the reference's teaching. It is respectfully submitted that no such teaching exists in the references cited by the current Office Action either alone or in any combination. There is nothing in the references' teachings suggesting the modification or the desirability of the modification. There is no evidence in the Office Action

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showing why a skilled artisan would have combined the cited references and then would have arrived at the present invention.

There must be some teaching, suggestion, or incentive in the references (and not Applicant's disclosure) that supports the combination of the references. *In re Fine*, 5 U.S.P.Q. 2d 1596, 1599-1600 (Fed. Cir. 1988). No such teaching, suggestion or incentive is in the cited documents.

According to the Board of Patent Appeals and Interferences in the case of *Ex parte Obukowicz*, 27 U.S.P.Q.2d 1063, 1065 (B.P.A.I. 1992) (with emphasis added):

In proceedings before the Patent and Trademark Office, the Examiner bear the burden of establishing a *prima facie* case of obviousness based upon the prior art. *In re Piasecki*, 745 F.2d 1468, 1471-72, 223 U.S.P.Q. 785, 787-88 (Fed. Cir. 1984).

The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Indeed, the teachings of references can be combined only if there is some suggestion or incentive to do so. *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 723 F.2d 1572, 1577, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984).

The picking and choosing from both of the cited references to allege that the instant invention is obvious simply fails in light of the case law under § 103. The Examiner is respectfully invited to cite references for the desirability of modification and the teaching, suggestion or incentive for combination and for modification of the reference teachings or provide an affidavit, as called for by 37 C.F.R. §1.106(b) and M.P.E.P. §706.02(a). Otherwise, it is respectfully submitted that the § 103 rejection must be withdrawn.

Accordingly, none of cited references, alone, or in any combination, render Applicant's invention *prima facie* obvious. Moreover, none of the references teach or suggest

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the surprising properties of the presently claimed invention, in particular that EPO can be administered to patients with RBV-induced anemia to allow patients to take the maximum effective dosage of RBV necessary to eradicate hepatitis C, which Applicant submits are additionally demonstrative of the patentability of the instant invention.

Consequently, the present invention is non-obvious and patentable over Bruchfeld and Niitsu, either alone or in any combination since the deficiencies of either reference are not remedied by the other.

Applicant therefore respectfully requests that the rejections under 35 U.S.C. §103(a) to claims 2-5 and 7-11 based on Bruchfeld either alone or in combination with Niitsu be withdrawn.

Claim 6 is objected to for depending from a rejected claim. In view of the claim amendment to claim 4, the objection is moot.

In view of these amendments and remarks, Applicant respectfully submits that all of the claims (claims 1 to 11 and 13 to 26) now pending in the application are in condition for allowance.

In view of the amendments and remarks herewith, the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance, or an interview at an early date with a view to placing the application in condition for allowance, are earnestly solicited.

Any additional fee occasioned by this paper or the claims herein, or any overpayment therein, may be charged or credited to Deposit Account No. 50-0320.


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If any issue remains as an impediment to allowance, an interview is respectfully requested prior to issuance of any paper other than a Notice of Allowance. The Examiner is respectfully requested to telephone the undersigned to arrange a mutually convenient time and manner for the interview. The Examiner is also respectfully requested to telephone the undersigned if there are any minor, formal issues that need resolving prior to issuance of a Notice of Allowance

Respectfully submitted,

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